Protective Groups in Organic Synthesis, Third Edition. Theodora W. Greene, Peter G.M. Wuts

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PROTECTION FOR THE THIOL GROUP

Protection for the thiol group is important in many areas of organic research, particularly in peptide and protein syntheses, which often involve the amino acid cysteine, $HSCH_2CH(NH_2)CO_2H$, CySH.[1] Protection of the thiol group in β-lactam chemistry has been reviewed.[2] The synthesis[3] of coenzyme A, which converts a carboxylic acid into a thioester, an acyl transfer agent in the biosynthesis or oxidation of fatty acids, also requires the use of thiol protective groups. A free –SH group can be protected as a thioether or a thioester, or oxidized to a symmetrical disulfide, from which it is regenerated by reduction. Thioethers are, in general, formed by reaction of the thiol, in a basic solution, with a halide; they are cleaved by reduction with sodium/ammonia, by acid-catalyzed hydrolysis, or by reaction with a heavy metal ion such as silver(I) or mercury(II), followed by hydrogen sulfide treatment. Some groups, including *S*-diphenylmethyl and *S*-triphenylmethyl thioethers and *S*-2-tetrahydropyranyl and *S*-isobutoxymethyl hemithioacetals, can be oxidized by thiocyanogen, $(SCN)_2$, iodine, or a sulfenyl chloride to a disulfide that is subsequently reduced to the thiol. Thioesters are formed and cleaved in the same way as oxygen esters; they are more reactive to nucleophilic substitution, as indicated by their use as "activated esters." Several miscellaneous protective groups, including thiazolidines, unsymmetrical disul-

fides, and *S*-sulfenyl derivatives, have been used to a more limited extent. This chapter discusses some synthetically useful thiol protective groups.[4,5] Some of the more useful groups are included in Reactivity Chart 7.

1. For a review on cysteine protection, see F. Cavelier, J. Daunis, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 210 (1990); see also reference 22 (**Peptides**) in Chapter 1.
2. H. Wild, "Protective Groups in β-Lactam Chemistry," in *The Organic Chemistry of β-Lactams*, G. I. Georg, Ed., VCH Publishers, 1993, pp. 1–48.
3. J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 663 (1961).
4. See also Y. Wolman, "Protection of the Thiol Group," in *The Chemistry of the Thiol Group*, S. Patai, Ed., Wiley-Interscience, New York, 1974, Vol. 15/2, pp. 669–684; R. G. Hiskey, V. R. Rao, and W. G. Rhodes, "Protection of Thiols," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum Press, New York and London, 1973, pp. 235–308.
5. R. G. Hiskey, "Sulfhydryl Group Protection in Peptide Synthesis," in *The Peptides*, E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1981, Vol. 3, pp. 137–167.

THIOETHERS

S-Benzyl and substituted *S*-benzyl derivatives, readily cleaved with sodium/ammonia, are the most frequently used thioethers. *n*-Alkyl thioethers are difficult to cleave and have not been used extensively as protective groups. Alkoxymethyl or alkylthiomethyl hemithio- or dithioacetals ($RSCH_2OR'$ or $RSCH_2SR'$) can be cleaved by acidic hydrolysis and by reaction with silver or mercury salts, respectively. Mercury(II) salts also cleave dithioacetals ($RS-CH_2SR'$), *S*-triphenylmethyl thioethers ($RS-CPh_3$), *S*-diphenylmethyl thioethers ($RS-CHPh_2$), *S*-acetamidomethyl derivatives ($RS-CH_2NHCOCH_3$), and *S*-(*N*-ethylcarbamates) (RS–CONHEt). *S*-*t*-Butyl thioethers (RS–*t*-Bu) are cleaved if refluxed with mercury(II); *S*-benzyl thioethers ($RS-CH_2Ph$) are cleaved if refluxed with mercury (II)/1 *N* HCl. Some β-substituted *S*-ethyl thioethers are cleaved by reactions associated with the β-substituent.

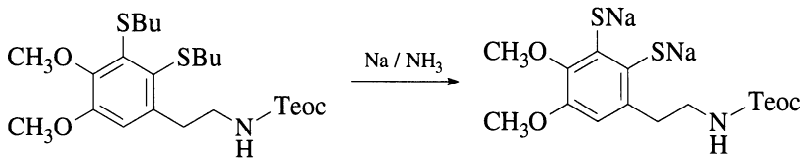
S-Alkyl Thioethers: $C_nH_{2n+1}SR$

Formation

1. *S*,*S*-Diphenyl-*S*-methoxythiazyne, benzene, 30° was used to prepare the methyl thioether.[1]
2. One of the simplest methods for preparation is by reaction of the thiol with KOH and RX in ethanol as solvent.
3. In many cases, a thiol group is introduced into a substrate through the use of a thiol (e.g., monoprotected H_2S), by a simple displacement or an addition reaction.[2]

Cleavage

1. Na/NH_3, >54% yield. Methyl thioether cleavage of BOC-protected methionine. [3]
2. Na/NH_3[4].



1. T. Yoshimura, E. Tsukurimichi, Y. Sugiyama, H. Kita, C. Shimasaki, and K. Hasegawa, *Bull. Chem. Soc. Jpn.*, **64**, 3176 (1991).
2. For a review, see J. L. Wardell, in *The Chemistry of the Thiol Group, Pt. 1,* S. Patai, Ed., Wiley, New York, 1974, pp. 179–211.
3. R. Lutgring, K. Sujatha, and J. Chmielewski, *Bioorg. Med. Chem. Lett.*, **3**, 739 (1993).
4. P. W. Ford, M. R. Narbut, J. Belli, and B. S. Davidson, *J. Org. Chem.*, **59**, 5955 (1994).

S-Benzyl Thioether: $RSCH_2Ph$ (Chart 7)

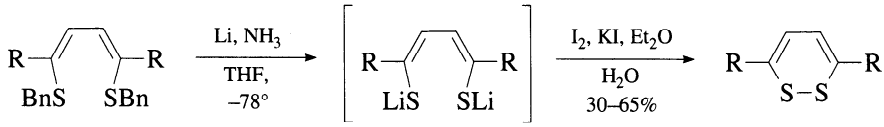
For the most part, cysteine and its derivatives have been protected by the reactions that follow.

Formation

1. $PhCH_2Cl$, 2 *N* NaOH or NH_3, EtOH, 30 min, 25°, 90% yield.[1]
2. $PhCH_2Cl$, Cs_2CO_3, DMF, 20°.[2]
3. $PhCH_2Br$, *n*-BuLi, THF, 0°–rt, 30 min, 85% yield.[3]

Cleavage

1. Na, NH_3, 10 min.[4]
2. Sodium in boiling butyl alcohol[5] or in boiling ethyl alcohol[6] can be used if the benzyl thioether is insoluble in ammonia.
3. Li, NH_3, THF, −78°.[7]



In this case, the use of Na/NH_3 was slow.

4. HF, anisole, 25°, 1 h.[8] The authors list 15 protective groups that are cleaved by this method, including some branched-chain carbonates and esters,

benzyl esters and ethers, the nitro-protective group in arginine, and *S*-benzyl and *S*-*t*-butyl thioethers. They report that 12 protective groups, including some straight-chain carbonates and esters, *N*-benzyl derivatives, and *S*-methyl, *S*-ethyl, and *S*-isopropyl thioethers, are stable under these conditions.

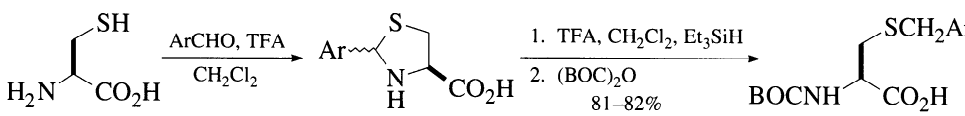
5. 5% Cresol, 5% thiocresol, 90% HF.[9] In the HF deprotection of thioethers and many other protective groups, anisole serves as a scavenger for the liberated cation formed during the deprotection process. If cations liberated during this deprotection are not scavenged, they can react with other amino acid residues, especially tyrosine. Dimethyl sulfide, thiocresol, cresol, and thioanisole have also been used as scavengers when strong acids are used for deprotection. A mixture of 5% cresol, 5% *p*-thiocresol, and 90% HF is recommended for benzyl thioether deprotection.[9] These conditions cause cleavage by an S_N1 mechanism. The use of low concentrations of HF in dimethyl sulfide (1:3), which has been recommended for the deprotection of other peptide protective groups, does not cleave the ***S*-4-methylbenzyl** group. Reactions that use low HF concentrations are considered to proceed via an S_N2 mechanism. The use of low HF concentrations with thioanisole results in some methylation of free thiols. The use of HF in anisole can also result in alkylation of methionine.
6. Electrolysis, NH_3, 90 min.[10]
7. Electrolysis, –2.8 V, DMF, $R_4N^+X^-$, 82% yield.[11,12]
8. Ph_2SO, $MeSiCl_3$, TFA, 4°, 4 h, 94% yield. The disulfide is formed.[13]
9. Bu_3SnH, AIBN, PhH, 3 h, Δ, >72% yield. The thiol is released as a stannyl sulfide that was used directly in a glycosylation.[14]

1. M. Frankel, D. Gertner, H. Jacobson, and A. Zilkha, *J. Chem. Soc.*, 1390 (1960); M. Dymicky and D. M. Byler, *Org. Prep. Proced. Int.*, **23**, 93 (1991).
2. F. Vögtle and B. Klieser, *Synthesis*, 294 (1982).
3. J. Yin and C. Pidgeon, *Tetrahedron Lett.*, **38**, 5953 (1997).
4. J. E. T. Corrie, J. R. Hlubucek, and G. Lowe, *J. Chem. Soc., Perkin Trans. 1*, 1421 (1977).
5. W. I. Patterson and V. du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).
6. K. Hofmann, A. Bridgwater, and A. E. Axelrod, *J. Am. Chem. Soc.*, **71**, 1253 (1949).
7. M. Koreeda and W. Yang, *Synlett*, 201 (1994).
8. S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967).
9. W. F. Heath, J. P. Tam, and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **28**, 498 (1986).
10. D. A. J. Ives, *Can. J. Chem.*, **47**, 3697 (1969).
11. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).
12. C. M. Delerue-Matos, A. M. Freitas, H. L. S. Maia, M. J. Medeiros, M. I. Montenegro, and D. Pletcher, *J. Electroanal. Chem. Interfacial Electrochem.*, **315**, 1 (1991).

13. T. Koide, A. Otaka, H. Suzuki, and N. Fujii, *Synlett*, 345 (1991); K. Akaji, T. Tatsumi, M. Yoshida, T. Kimura, Y. Fujiwara, and Y. Kiso, *J. Chem. Soc., Chem. Comm.*, 167 (1991).
14. W. P. Neumann, *Synthesis*, 665 (1987); H.-S. Byun and R. Bittman, *Tetrahedron Lett.*, **36**, 5143 (1995).

S-*p*-Methoxybenzyl Thioether: $RSCH_2C_6H_4$–*p*-OCH_3 (Chart 7)

Formation

1. 4-$MeOC_6H_4CH_2Cl$, NH_3, 78% yield.[1]
2. 4-$MeOC_6H_4CH_2Cl$, Na/NH_3, 87% yield.[2]
3. 4-$MeOC_6H_4CH_2OH$, TFA, CH_2Cl_2, 37–81% yield.[3]
4. 

Ar = 4-$MeOC_6H_4$, Ph, 4-MeC_6H_4

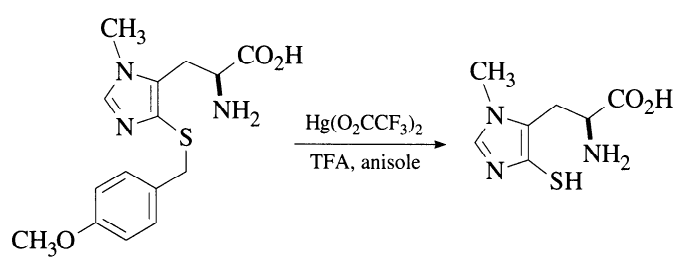
Ref. 3

5. 4-$MeOC_6H_4CH_2Cl$, NaH, THF, 60°, 1 h.[4]

Cleavage

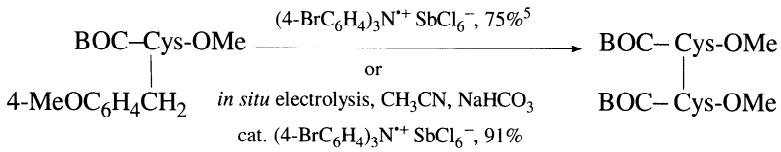
An *S*-4-methoxybenzyl thioether is stable to HBr/AcOH[1] and to I_2/MeOH.[5] The latter reagent cleaves *S*-trityl and *S*-diphenylmethyl groups.

1. $Hg(OAc)_2$, CF_3COOH, 0°, 10–30 min, or $Hg(OCOCF_3)_2$, aq. AcOH, 20°, 2–3 h, followed by H_2S or $HSCH_2CH_2OH$, 100% yield.[6,7] An *S*-*t*-butyl thioether is cleaved in quantitive yield under these conditions.
2. $Hg(OCOCF_3)_2$, CF_3COOH, anisole.[8] The **dimethoxybenzyl** thioether is also cleaved with this reagent.[9]

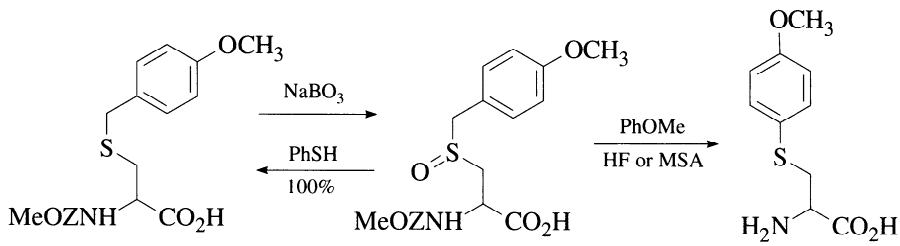


3. CF_3COOH, reflux.[1]
4. CF_3COOH, *o*-cresol, reflux, 24 h, >52% yield.[10]
5. Anhydrous HF, anisole, 25°, 1 h, quant.[11]

6.



7. During the synthesis of peptides that contain 4-methoxybenzyl-protected cysteine residues, sulfoxide formation may occur. These sulfoxides, when treated with HF/anisole, form thiophenyl ethers that cannot be deprotected; therefore, the peptides should be subjected to a reduction step prior to deprotection.[12]



MSA = methanesulfonic acid

Note the missing methylene

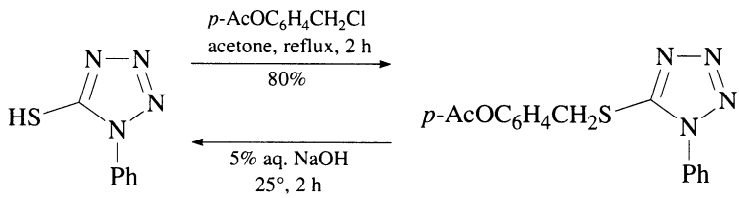
8. $AgBF_4$, anisole, TFA, 4°, 1 h, 87% conversion.[13]
9. $MeSiCl_3$, Ph_2SO, TFA, 4°, 10 min, 95% conversion to cystine.[14]

1. S. Akabori, S. Sakakibara, Y. Shimonishi, and Y. Nobuhara, *Bull. Chem. Soc. Jpn.*, **37**, 433 (1964).
2. M. D. Bachi, S. Sasson, and J. Vaya, *J. Chem. Soc., Perkin Trans.1*, 2228 (1980).
3. L. S. Richter, J. C. Marster, Jr., and T. R. Gadek, *Tetrahedron Lett.*, **35**, 1631 (1994).
4. A. W. Tayor and D. K. Dean, *Tetrahedron Lett.*, **29**, 1845 (1988).
5. M. Platen and E. Steckhan, *Liebigs Ann. Chem.*, 1563 (1984).
6. O. Nishimura, C. Kitada, and M. Fujino, *Chem. Pharm. Bull.*, **26**, 1576 (1978).
7. E. M. Gordon, J. D. Godfrey, N. G. Delaney, M. M. Asaad, D. Von Langen, and D. W. Cushman, *J. Med. Chem.*, **31**, 2199 (1988).
8. T. P. Holler, A. Spaltenstein, E. Turner, R. E. Klevit, B. M. Shapiro, and P. B. Hopkins, *J. Org. Chem.*, **52**, 4420 (1987).
9. N. Shibata, J. E. Baldwin, A. Jacobs, and M. E. Wood, *Tetrahedron*, **52**, 12839 (1996).
10. R. Lutgring, K. Sujatha, and J. Chmielewski, *Bioorg. Med. Chem. Lett.*, **3**, 739 (1993).
11. S. Sakakibara and Y. Shimonishi, *Bull. Chem. Soc. Jpn.*, **38**, 1412 (1965).
12. S. Funakoshi, N. Fujii, K. Akaji, H. Irie, and H. Yajima, *Chem. Pharm. Bull.*, **27**, 2151 (1979).

13. M. Yoshida, T. Tatsumi, Y. Fujiwara, S. Iinuma, T. Kimura, K. Akaji, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 1551 (1990).
14. K. Akaji, T. Tatsumi, M. Yoshida, T. Kimura, Y. Fujiwara and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, 167 (1991).

S-o- or *p*-Hydroxy- or Acetoxybenzyl Thioether:
$RSCH_2C_6H_4$–*o*-(or *p*-)-OR′: R′ = H or Ac

Formation/Cleavage[1]



The cleavage process occurs by *p*-quinonemethide formation after acetate hydrolysis.

1. L. D. Taylor, J. M. Grasshoff, and M. Pluhar, *J. Org. Chem.*, **43**, 1197 (1978); J. B. Christensen, *Org. Prep. Proced. Int.*, **26**, 471 (1994); C. Gemmell, G. C. Janairo, J. D. Kilburn, H. Ueck, and A. E. Underhill, *J. Chem. Soc., Perkin Trans. 1*, 2715 (1994).

S-p-Nitrobenzyl Thioether: $RSCH_2C_6H_4$–*p*-NO_2 (Chart 7)

Formation

1. 4-$NO_2C_6H_4CH_2Cl$, 1 *N* NaOH, 0°, 1 h → 25°, 0.5 h[1] or NaH, $PhCH_3$, 68% yield.[2]

Cleavage

1. H_2, Pd–C, HCl or AcOH, 7–8 h, 60–68%; $HgSO_4$, H_2SO_4, 20 h, 60%; H_2S, 15 min., 60% yield[2] or RSSR, 76% yield after air oxidation.[1] Hydrogenation initially produces the *p*-amino derivative that is then cleaved with Hg(II).

1. M. D. Bachi and K. J. Ross-Petersen, *J. Org . Chem.*, **37**, 3550 (1972).
2. M. D. Bachi and K. J. Ross-Petersen, *J. Chem. Soc., Chem. Commun.*, 12 (1974).

S-2,4,6-Trimethylbenzyl Thioether: 2,4,6-$Me_3C_6H_2$ CH_2SR

Formation

1. From cysteine: Na/NH_3, 2,4,6-$Me_3C_6H_2CH_2Cl$, 57% yield.[1]

Cleavage

1. HF, anisole, 0°, 30 min or TfOH, TFA, anisole, 30 min. This group is stable to refluxing TFA, whereas the more frequently used 4-methoxybenzyl group is not.[1]
2. Me_2Se, HF, *m*-cresol, 0°, 60 min. These conditions are also excellent for reduction of methionine sulfoxide [Met(O)].[2]
3. $AgBF_4$, anisole, TFA, 4°, 1 h, 73% conversion.[3]

1. F. Brtnik, M. Krojidlo, T. Barth, and K. Jost, *Collect. Czech. Chem. Commun.*, **46**, 286 (1981).
2. M. Yoshida, M. Shimokura, Y. Fujiwara, T. Fujisaki, K. Akaji, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 382 (1990).
3. M. Yoshida, T. Tatsumi, Y. Fujiwara, S. Iinuma, T. Kimura, K. Akaji, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 1551 (1990).

S-2,4,6-Trimethoxybenzyl Thioether (Tmob–SR): $2,4,6\text{-}(MeO)_3C_6H_2CH_2SR$

Formation

1. $2,4,6\text{-}(MeO)_3C_6H_2CH_2OH$, TFA, CH_2Cl_2, 84% yield.[1]

Cleavage

1. 5% H_2O, 5% phenol, 5% thioanisol in TFA/CH_2Cl_2 (30% v/v).[1]
2. TFA, CH_2Cl_2, triisopropylsilane or triethylsilane, 30 min, 25°.[1]
3. $Tl(TFA)_3$, DMF, anisole, 0°, 90 min.[1,2]

1. M. C. Munson, C. Garcia-Escheverria, F. Albericio, and G. Barany, *J. Org. Chem.*, **57**, 3013 (1992).
2. M. C. Munson, C. Garcia-Echeverría, F. Albericio, and G. Barany, *Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th*, 605 (1992).

S-4-Picolyl Thioether: $RSCH_2$–4-pyridyl (Chart 7)

Formation

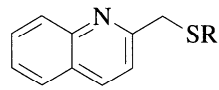
1. 4-Picolyl chloride, 60% yield.[1]

Cleavage

1. Electrolytic reduction, 0.25 *M* H_2SO_4, 88% yield. *S*-4-Picolylcysteine is stable to CF_3COOH (7 days), to HBr/AcOH, and to 1 *M* NaOH. References for the electrolytic removal of seven other protective groups are included.[1,2]

1. A. Gosden, R. Macrae, and G. T. Young, *J. Chem. Res., Synop.*, 22 (1977).

2. C. M. Delerue-Matos, A. M. Freitas, H. L. S. Maia, M. J. Medeiros, M. I. Montenegro, and D. Pletcher, *J. Electroanal. Chem. Interfacial Electrochem.*, **315**, 1 (1991).

S-2-Quinolinylmethyl Thioether (Qm–SR): 

Formation

1. QmCl, NaH or NaOH or TEA, EtOH, 74% from cysteine.[1]

Cleavage

1. $FeCl_3$ or $CuCl_2$, DMF, H_2O, 61–99% yield, isolated as the disulfide. The quinoline group is isolated as the aldehyde.[1]

1. H. Yoshizawa, A. Otaka, H. Habashita, and N. Fujii, *Chem. Lett.*, 803 (1993).

S-2-Picolyl *N*-Oxide Thioether: $RSCH_2$–2-pyridyl *N*-Oxide (Chart 7)

Formation

1. 2-Picolyl chloride *N*-oxide, aq. NaOH, moderate yields.[1]

Cleavage

1. Ac_2O, reflux, 7 min or 25°, 1.5 h followed by hydrolysis; aq. NaOH, 25°, 3–12 h, 79% yield.[1]
2. Electrolysis on a glassy carbon electrode, DMF, $Bu_4N^+BF_4^-$, 85% yield.[2]

1. Y. Mizuno and K. Ikeda, *Chem. Pharm. Bull.*, **22**, 2889 (1974).
2. M. D. Geraldo and M. J. Medeiros, *Port. Electrochim. Acta*, **9**, 175 (1991).

S-9-Anthrylmethyl Thioether: $RSCH_2$–9-anthryl (Chart 7)

Formation

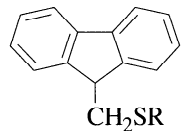
1. 9-Anthrylmethyl chloride, DMF, −20°, N_2.[1]

Cleavage

1. CH_3SNa, DMF or HMPA, 0–25°, 2–5 h, 68–92% yield.[1]

1. N. Kornblum and A. Scott, *J. Am. Chem. Soc.*, **96**, 590 (1974).

S-9-Fluorenylmethyl Thioether (Fm–SR):



Formation

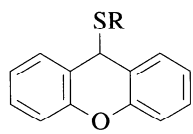
1. Et(*i*-Pr)$_2$N, DMF, FmCl.[1]
2. FmOTs, DMF, 0°–25°, 71%. This procedure has the advantage that FmOTs is prepared in 83% yield from FmOH, whereas the chloride, FmCl, is produced in only 30% yield from the alcohol and $SOCl_2$.[2]

Cleavage

1. 50% Piperidine, DMF or NH_4OH, 2 h.[3] The *S*-fluorenylmethyl group is stable to 95% HF/5% anisole for 1 h at 0°, to trifluoroacetic acid, to 12 *N* HCl, to 0.1 *M* I_2 in DMF, and to CF_3SO_3H in CF_3COOH.[2]
2. $(Me_2N)_2C{=}N{-}t\text{-}Bu$, 23°.[4]

1. M. Bodanszky and M. A. Bednarek, *Int. J. Pept. Protein Res.*, **20**, 434 (1982).
2. F. Albericio, E. Nicolas, J. Rizo, M. Ruiz-Gayo, E. Pedroso, and E. Giralt, *Synthesis*, 119 (1990).
3. M. Ruiz-Gayo, F. Albericio, E. Pedroso, and E. Giralt, *J. Chem. Soc., Chem. Commun.*, 1501 (1986).
4. E. J. Corey, D. Y. Gin, and R. S. Kania, *J. Am. Chem. Soc.*, **118**, 9202 (1996).

S-Xanthenyl Thioether (Xan–SR):



Formation

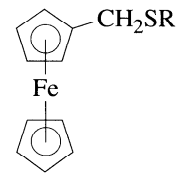
1. 9*H*-Xanthen-9-ol, TFA, CH_2Cl_2, 25°, 30 min.[1] The 2-methoxy analogue can be prepared similarly, and it is cleaved only slightly faster than the unsubstituted derivative.

Cleavage[1]

1. 0.2% TFA, CH_2Cl_2, Et_3SiH. Other scavengers are not nearly as effective, but when the xanthenyl group is used on a solid phase, more acid is required to get efficient cleavage.
2. I_2, MeOH, DMF or AcOH. AcOH is the most effective solvent, 67–100% yield.
3. $Tl(TFA)_3$, DMF, MeOH, CH_2Cl_2, or acetic acid, 94–100% yield.

1. Y. Han and G. Barany, *J. Org. Chem.*, **62**, 3841 (1997).

S-Ferrocenylmethyl Thioether (Fcm–SR):



Formation

1. Cp–Fe–$CpCH_2OH$, TFA, acetone, H_2O, rt, overnight, 96% yield.[1]

Cleavage

The Fcm group can be removed with TFA, Ag(I), or Hg(II). The use of scavengers such as thiophenol and anisole is recommended. The Fcm group is stable to mild acid and base, but it is not stable to electrophilic reagents such as $(SCN)_2$, I_2/AcOH, or carboxymethylsulfenyl chloride (CmsCl).[1]

1. A. S. J. Stewart and C. N. C. Drey, *J. Chem. Soc., Perkin Trans. 1*, 1753 (1990).

S-Diphenylmethyl, Substituted S-Diphenylmethyl, and S-Triphenylmethyl Thioethers

S-Diphenylmethyl, substituted *S*-diphenylmethyl, and *S*-triphenylmethyl thioethers have often been formed or cleaved by the same conditions, although sometimes in rather different yields. As an effort has been made to avoid repetition in the sections that describe these three protective groups, the reader should glance at all the sections.

S-Diphenylmethyl Thioether: $RSCH(C_6H_5)_2$ (Chart 7)

Formation

1. Ph_2CHOH, CF_3COOH, 25°, 15 min or Ph_2CHOH, HBr, AcOH, 50°, 2 h, >90% yield.[1]
2. Boron trifluoride etherate (in HOAc, 60–80°, 15 min, high yields)[2] also catalyzes the formation of *S*-diphenylmethyl and *S*-triphenylmethyl thioethers from aralkyl alcohols.
3. Yields of thioethers, formed under nonacidic conditions (Ph_2CHCl or Ph_3CCl, DMF, 80–90°, 2 h, N_2) are not as high ($RSCHPh_2$, 50% yield; $RSCPh_3$, 75% yield)[3] as the yields obtained under the acidic conditions described in items 1 and 2.

Cleavage

1. CF_3COOH, 2.5% phenol, 30°, 2 h, 65% yield.[1] Zervas and co-workers tried many conditions for the acid-catalyzed formation and removal of the *S*-diphenylmethyl, ***S*-4,4′-dimethoxydiphenylmethyl**, and *S*-triphenylmethyl thioethers. The best conditions for the *S*-diphenylmethyl thioether are those shown here. Phenol or anisole act as cation scavengers.
2. Na, NH_3, 97% yield.[3] Sodium/ammonia is an efficient, but nonselective, reagent. (RS–Ph, RS–CH_2Ph, RS–CPh_3, and RS–SR are also cleaved.)
3. 2-$NO_2C_6H_4SCl$, AcOH (results in disulfide formation), followed by $NaBH_4$ or $HS(CH_2)_2OH$ or dithioerythritol, quant.[4] *S*-Triphenylmethyl, *S*-4,4′-dimethoxydiphenylmethyl, and *S*-acetamidomethyl groups are also removed by this method.

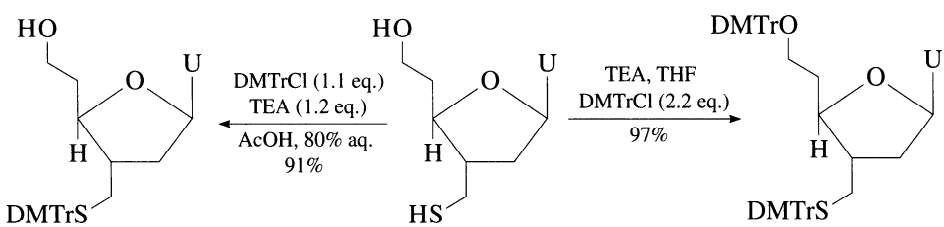
1. I. Photaki, J. T.-Papadimitriou, C. Sakarellos, P. Mazarakis, and L. Zervas, *J. Chem. Soc. C*, 2683 (1970).
2. R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, **30**, 1340 (1965).
3. L. Zervas and I. Photaki, *J. Am. Chem. Soc.*, **84**, 3887 (1962).
4. A. Fontana, *J. Chem. Soc., Chem. Commun.*, 976 (1975).

S-Bis(4-methoxyphenyl)methyl Thioether: RSCH(C_6H_4–4-OCH_3)$_2$ (Chart 7)

S-Bis(4-methoxyphenyl)phenylmethyl Thioether (DMTr)

Formation

1. DMTrCl (dimethoxytrityl chloride), TEA, 80% aq. AcOH, 91% yield.[1]

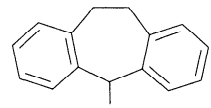


2. (4-$MeOC_6H_4$)$_2$CHCl, DMF, 25°, 2 days, 96% yield.[2]

Cleavage

1. Selective cleavage of the DMTr group from oxygen is accomplished with 80% aq. AcOH (rt, 10 min), whereas selective cleavage of the DMTr group from the thiol is effected with $AgNO_3$/NaOAc buffer (rt, 1 min).[1]
2. HBr, AcOH, 50–60°, 30 min, or CF_3COOH, phenol, reflux, 30 min, quant.[2]

1. Z. Huang and S. A. Benner, *Synlett*, 83 (1993).
2. R. W. Hanson and H. D. Law, *J. Chem. Soc.*, 7285 (1965).

S-5-Dibenzosuberyl Thioether: 

5-Dibenzosuberyl alcohol reacts in 60% yield with cysteine to give a thioether that is cleaved by mercury(II) acetate or oxidized by iodine to cystine. The dibenzosuberyl group has also been used to protect –OH, $-NH_2$, and $-CO_2H$ groups.[1]

1. J. Pless, *Helv. Chim. Acta*, **59**, 499 (1976).

S-Triphenylmethyl Thioether: $RSC(C_6H_5)_3$ (Chart 7)

S-Triphenylmethyl thioethers have been formed by reaction of the thiol with triphenylmethyl alcohol/anhydrous CF_3COOH (85–90% yield) or with triphenylmethyl chloride (75% yield). Glycosidic triphenylmethyl thioethers are prepared by displacement of the chloride with $TrS^-\ {}^+N(Bu)_4$ (tetrabutylammonium triphenylmethanethiolate).[1]

Cleavage

1. HCl, aq. AcOH, 90°, 1.5 h.[2]
2. $Hg(OAc)_2$, EtOH, reflux, 3 h, → 25°, 12 h; H_2S, 61% yield.[2]
3. $AgNO_3$, EtOH, Pyr, 90°, 1.5 h; H_2S, 47% yield.[2] DTE (dithioerythritol) and NaOAc in MeOH/THF can be used in place of H_2S (97% yield).[3] An *S*-triphenylmethyl thioether can be selectively cleaved in the presence of an *S*-diphenylmethyl thioether by acidic hydrolysis or by heavy-metal ions. As a result of the structure of the substrate, the relative yields of cleavage by $AgNO_3$ and $Hg(OAc)_2$ can be reversed.[4]
4. Thiocyanogen [$(SCN)_2$, 5°, 4 h, 40% yield] selectively oxidizes an *S*-triphenylmethyl thioether to the disulfide (RSSR) in the presence of an *S*-diphenylmethyl thioether.[5]
5. *S*-Triphenylmethylcysteine is readily oxidized by iodine (MeOH, 25°) to cystine.[6,7] The *S*-triphenylmethylcysteine group can be selectively cleaved in the presence of a –Cys(Acm)– group (Acm = acetamidomethyl).[8] *S*-Benzyl and *S*-*t*-butyl thioethers are stable to the action of iodine.
6. Electrolysis, –2.6 V, DMF, $R_4N^+X^-$.[9]
7. Et_3SiH, 50% TFA, CH_2Cl_2, 1 h, rt.[10]
8. PhHgOAc 1.2 eq., MeOH–CH_2Cl_2 (4:1), 96% yield. The resulting Hg salt is liberated with H_2S.[1]

1. M. Blanc-Muesser, L. Vigne, and H. Driquez, *Tetrahedron Lett.*, **31**, 3869 (1990).

2. R. G. Hiskey, T. Mizoguchi, and H. Igeta, *J. Org. Chem.*, **31**, 1188 (1966).
3. Z. Huang and S. A. Benner, *Synlett*, 83 (1993).
4. R. G. Hiskey and J. B. Adams, *J. Org. Chem.*, **31**, 2178 (1966).
5. R. G. Hiskey, T. Mizoguchi, and E. L. Smithwick, *J. Org. Chem.*, **32**, 97 (1967).
6. B. Kamber, *Helv. Chim. Acta*, **54**, 398 (1971).
7. K. W. Li, J. Wu, W. Xing, and J. A. Simon, *J. Am. Chem. Soc.*, **118**, 7237 (1996).
8. B. Kamber, A. Hartmann, K. Eisler, B. Riniker, H. Rink, P. Sieber, and W. Rittel, *Helv. Chim. Acta*, **63**, 899 (1980).
9. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).
10. D. A. Pearson, M. Blanchette, M. L. Baker, and C. A. Guindon, *Tetrahedron Lett.*, **30**, 2739 (1989).

S-Diphenyl-4-pyridylmethyl Thioether: $RSC(C_6H_5)_2$–4-pyridyl

Formation

1. $Ph_2(4\text{-}C_5H_4N)COH$, $BF_3{\cdot}Et_2O$, AcOH, 60°, 48 h.[1]

Cleavage

1. $Hg(OAc)_2$, AcOH, pH 4, 25°, 15 min.[1]
2. Zn, 80% AcOH, H_2O.[2]

The diphenylpyridylmethyl thioether is stable to acids (e.g., CF_3COOH, 21°, 48 h; 45% HBr/AcOH, 21°); it is oxidized by iodine to cystine (91%) or reduced by electrolysis at a mercury cathode.[1]

1. S. Coyle and G. T. Young, *J. Chem. Soc., Chem. Commun.*, 980 (1976).
2. S. Coyle, A. Hallett, M. S. Munns, and G. T. Young, *J. Chem. Soc., Perkin Trans. 1*, 522 (1981).

S-Phenyl Thioether: RSC_6H_5

Although a sulfhydryl group generally is not converted to an *S*-phenyl thioether, the conversion can be accomplished through the use of a Pd-catalyzed arylation with an aryl iodide.[1] Thiophenol can be used to introduce sulfur into molecules by simple displacement or by Michael additions, and thus, the phenyl group serves as a suitable protective group that can be removed by electrolysis (–2.7 V, DMF, $R_4N^+X^-$).[2]

1. P. G. Ciattini, E. Morera, and G. Ortar, *Tetrahedron Lett.*, **36**, 4133 (1995).
2. V. G. Mairanovsky, *Angew. Chem., Int. Ed., Engl.*, **15**, 281 (1976).

S-2,4-Dinitrophenyl Thioether: RSC_6H_3–2,4-$(NO_2)_2$ (Chart 7)

Formation

1. 2,4-$(NO_2)_2$–C_6H_3F, base.[1] The sulfhydryl group in cysteine can be selectively protected in the presence of the amino group by reaction with 2,4-dinitrophenol at pH 5–6.[2]

Cleavage

1. $HSCH_2CH_2OH$, pH 8, 22°, 1 h, quant.[1]

1. S. Shaltiel, *Biochem. Biophys. Res. Commun.*, **29**, 178 (1967).
2. H. Zahn and K. Traumann, *Z. Naturforsch.*, **9B**, 518 (1954).

S-*t*-Butyl Thioether: $RSC(CH_3)_3$ (Chart 7)

Formation

1. Isobutylene, H_2SO_4, CH_2Cl_2, 25°, 12 h, 73% yield.[1] The *S*-*t*-butyl derivative of cysteine is stable to HBr/AcOH and to CF_3COOH.
2. *t*-BuOH, 2 *N* HCl, reflux, 90% yield.[2]
3. *t*-BuOH, H_2SO_4, H_2O, 0°, 0.5 h and rt, 2 h, 98%.[3] A carboxylic acid was left unprotected under these conditions.

Cleavage

1. $Hg(OAc)_2$, CF_3COOH, anisole, 0°, 15 min; H_2S, quant.[4]
2. $Hg(OCOCF_3)_2$, aq. AcOH, 25°, 1 h; H_2S, quant.[4]
3. HF, anisole, 20°, 30 min.[5] No cleavage is observed with HF, *m*-cresol.[6]
4. 2-$NO_2C_6H_4SCl$; $NaBH_4$.[2] Treatment of the thioether with the sulfenyl chloride initially produces a disulfide, which is then reduced to afford the free thiol.
5. Tetramethylene sulfoxide, TMSOTf, 4°, 4 h, 87% yield or Ph_2SO, $MeSiCl_3$ or $SiCl_4$, TFA, 90–96% yield. The latter conditions also cleave the Acm, Bn, MeOBn, and MeBn groups. In all cases, disulfides are isolated.[7]

1. F. M. Callahan, G. W. Anderson, R. Paul, and J. E. Zimmerman, *J. Am. Chem. Soc.*, **85**, 201 (1963).
2. J. J. Pastuszak and A. Chimiak, *J. Org. Chem.*, **46**, 1868 (1981).
3. R. Breitschuh and D. Seebach, *Synthesis*, 83 (1992).
4. O. Nishimura, C. Kitada, and M. Fujino, *Chem. Pharm. Bull.*, **26**, 1576 (1978).
5. S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967).
6. K. Akaji, K. Fujino, T. Tatsumi, and Y. Kiso, *J. Am. Chem. Soc.*, **115**, 11384 (1993).

7. T. Koide, A. Otaka, H. Suzuki and N. Fujii, *Synlett*, 345 (1991).

S-1-Adamantyl Thioether: RS-1-adamantyl

Formation

1. 1-Adamantyl alcohol, CF_3COOH, 25°, 12 h, 90% yield.[1]
2. From a disulfide: $ArI(OCOAd)_2$, Hg $h\nu$, CH_2Cl_2.[2]

Cleavage

1. $Hg(OAc)_2$, CF_3COOH, 0°, 15 min, 100% yield.[1]
2. $Hg(OCOCF_3)_2$, aq. AcOH, 20°, 60 min, 100% yield.[1]
3. 1 *M* CF_3SO_3H, $PhSCH_3$ or $Tl(OCOCF_3)_3$.[3]

The *S*-adamantyl group is less prone to sulfoxide formation than the *S*-4-methoxybenzyl group. It is also more stable to CF_3COOH.

1. O. Nishimura, C. Kitada, and M. Fujino, *Chem. Pharm. Bull.*, **26**, 1576 (1978).
2. H. Togo, T. Muraki, and M. Yokoyama, *Synthesis*, 155 (1995).
3. N. Fujii, A. Otaka, S. Funakoshi, H. Yajima, O. Nishimura, and M. Fujino, *Chem. Pharm. Bull.*, **34**, 869 (1986); N. Fujii, H. Yajima, A. Otaka, S. Funakoshi, M. Nomizu, K. Akaji, I. Yamamoto, K. Torizuka, K. Kitagawa, T. Akita, K. Ando, T. Kawamoto, Y. Shimonishi, and T. Takao, *J. Chem. Soc., Chem. Commun.*, 602 (1985).

Substituted *S*-Methyl Derivatives

Monothio, Dithio, and Aminothio Acetals

S-Methoxymethyl Monothioacetal: $RSCH_2OCH_3$

Formation

1. Zn, $(CH_3O)_2CH_2$, $BrCH_2CO_2Et$, 80–82% yield. Formation of the methoxymethyl thioether with dimethoxymethane[1] avoids the use of the carcinogen chloromethyl methyl ether.[2] The reaction forms an intermediate zinc thiolate, which then forms the monothioacetal.
2. $ClCH_2Br$, KOH, $BnN^+Et_3Cl^-$, MeOH, 70–90% yield.[3]

1. F. Dardoize, M. Gaudemar, and N. Goasdoue, *Synthesis*, 567 (1977).
2. T. Fukuyama, S. Nakatsuka, and Y. Kishi, *Tetrahedron Lett.*, 3393 (1976).
3. F. D. Toste and I. W. J. Still, *Synlett*, 159 (1995).

S-Isobutoxymethyl Monothioacetal: $RSCH_2OCH_2CH(CH_3)_2$ (Chart 7)

Formation

1. $ClCH_2OCH_2CH(CH_3)_2$, 82% yield.[1]

Cleavage

1. 2 *N* HBr, AcOH, rapid.[1]

The *S*-isobutoxymethyl monothioacetal is stable to 2 *N* hydrochloric acid and to 50% acetic acid; some decomposition occurs in 2 *N* sodium hydroxide.[1] The monothioacetal is also stable to 12 *N* hydrochloric acid in acetone (used to remove an *N*-triphenylmethyl group) and to hydrazine hydrate in refluxing ethanol (used to cleave an *N*-phthaloyl group). It is cleaved by boron trifluoride etherate in acetic acid, by silver nitrate in ethanol, and by trifluoroacetic acid. The monothioacetal is oxidized to a disulfide by thiocyanogen, $(SCN)_2$.[2]

1. P. J. E. Brownlee, M. E. Cox, B. O. Handford, J. C. Marsden, and G. T. Young, *J. Chem. Soc.*, 3832 (1964).
2. R. G. Hiskey and J. T. Sparrow, *J. Org. Chem.*, **35**, 215 (1970).

S-Benzyloxymethyl Monothioacetal (BOM–SR): $BnOCH_2SR$

Formation

1. $BnOCH_2Cl$, 4 *N* NaOH, 2 h, 0°, 69% yield.[1]

Cleavage

1. AgOTf, TFA.[1]

1. A. Otaka, H. Morimoto, N. Fujii, T. Koide, S. Funakoshi, and H. Yajima, *Chem. Pharm. Bull.*, **37**, 526 (1989).

S-2-Tetrahydropyranyl Monothioacetal: RS-2-tetrahydropyranyl (Chart 7)

Formation

1. Dihydropyran, $BF_3{\cdot}Et_2O$, Et_2O, 0°, 0.5 h → 25°, 1 h, satisfactory yields.[1]
2. Dihydropyran, PPTS (pyridinium *p*-toluenesulfonate), 4 hr, 25°, 92% yield.[2]

Cleavage

1. Aqueous $AgNO_3$, 0°, 10 min, quant.[3]
2. HBr, CF_3COOH, 90 min, 100% yield.[4]

An *S*-tetrahydropyranyl monothioacetal is stable to 4 *N* HCl/CH_3OH, 0° and to reduction with Na/NH_3. (An *O*-tetrahydropyranyl acetal is cleaved by 0.1 *N* HCl,

22°, $t_{1/2}$ = 4 min.)[5] An *S*-2-tetrahydropyranyl monothioacetal is oxidized to a disulfide by iodine[3] or thiocyanogen, $(SCN)_2$.[6]

1. R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4789 (1962).
2. E. Block, V. Eswarakrishnan, M. Gernon, G. O.-Okai, C. Saha, K. Tang, and J. Zubieta, *J. Am. Chem. Soc.*, **111**, 658 (1989).
3. G. F. Holland and L. A. Cohen, *J. Am. Chem. Soc.*, **80**, 3765 (1958).
4. K. Hammerström, W. Lunkenheimer, and H. Zahn, *Makromol. Chem.*, **133**, 41 (1970).
5. B. E. Griffin, M. Jarman, and C. B. Reese, *Tetrahedron*, **24**, 639 (1968).
6. R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4794 (1962).

S-Benzylthiomethyl Dithioacetal: $RSCH_2SCH_2C_6H_5$

S-Phenylthiomethyl Dithioacetal: $RSCH_2SC_6H_5$

Formation

1. $ClCH_2SCH_2Ph$, NH_3, 91% yield.[1]

Cleavage

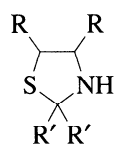
1. $Hg(OAc)_2$, H_2O, 80% AcOH, $HSCH_2CH_2SH$, 25°, 5–20 min; H_2S, 2 h, high yield.[1]

   The removal of an *S*-benzylthiomethyl protective group from a dithioacetal with mercury(II) acetate avoids certain side reactions that occur when an *S*-benzyl thioether is cleaved with sodium/ammonia. The dithioacetal is stable to hydrogen bromide/acetic acid used to cleave benzyl carbamates.

S-Phenylthiomethyl dithioacetals ($RSCH_2SC_6H_5$) were prepared and cleaved by similar methods.[1]

The dithioacetal is stable to catalytic reduction (H_2/Pd–C, CH_3OH–HOAc, 12 h, the conditions used to cleave a *p*-nitrobenzyl carbamate).[2]

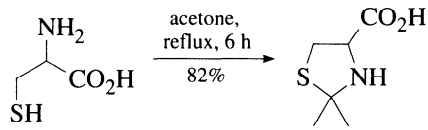
1. P. J. E. Brownlee, M. E. Cox, B. O. Handford, J. C. Marsden, and G. T. Young, *J. Chem. Soc.*, 3832 (1964).
2. R. Camble, R. Purkayastha, and G. T. Young, *J. Chem. Soc. C*, 1219 (1968).

Thiazolidine Derivative: 

Thiazolidines have been prepared from β-aminothiols—for example, cysteine—to protect the –SH and –NH groups during syntheses of peptides, including glutathione.[1] Thiazolidines are oxidized to symmetrical disulfides with iodine;[2] they do not react with thiocyanogen in a neutral solution.[3]

Formation[4]

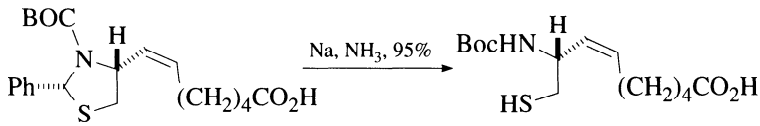
1.



Cleavage

1. HCl, H_2O, CH_3OH, 25°, 3 days, high yield.[4]
2. $HgCl_2$, H_2O, 25°, 2 days or 60–70°, 15 min; H_2S, 20 min, 30–40% yield.[4]
3. *N*-BOC thiazolidines can be cleaved with ScmCl (methoxycarbonylsulfenyl chloride) (AcOH, DMF, H_2O) to afford the Scm derivative in >90% yield.[5]

4.



1. F. E. King, J. W. Clark-Lewis, G. R. Smith, and R. Wade, *J. Chem. Soc.*, 2264 (1959).
2. S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).
3. R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4789 (1962).
4. J. C. Sheehan and D.-D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1158 (1958).
5. D. S. Kemp and R. I. Carey, *J. Org. Chem.*, **54**, 3640 (1989).

S-Acetamidomethyl Thioacetal (Acm–SR): $RSCH_2NHCOCH_3$ (Chart 7)

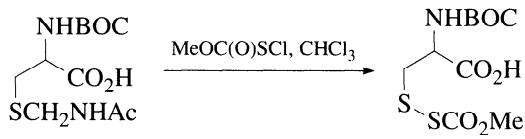
Formation

1. $AcNHCH_2OH$, concd. HCl, pH 0.5, 25°, 1–2 days, 52% yield.[1]
2. $AcNHCH_2OH$, TFA.[2]

Cleavage

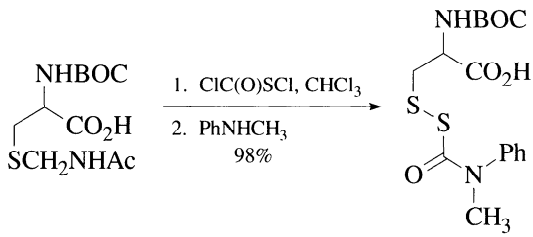
1. $Hg(OAc)_2$, pH 4, 25°, 1 h; H_2S; air, 98% yield of cystine.[1] An *S*-acetamidomethyl group is hydrolyzed by the strongly acidic (6 *N* HCl, 110°, 6 h) or strongly basic conditions used to cleave amide bonds. The group is stable to anhydrous trifluoroacetic acid and to hydrogen fluoride (0°, 1 h; 18°, 1 h, 10% cleaved). It is stable to zinc in acetic acid and to hydrazine in acetic acid or methanol.[1] If the Acm group is oxidized, there is no satisfactory method to liberate the cysteine. Cleavage of the sulfoxide with HF/anisole or CH_3SO_3H/anisole affords $Cys(C_6H_4OMe)$.[3]

2. 2-$NO_2C_6H_4SCl$, AcOH; $HO(CH_2)_2SH$ or $NaBH_4$, quant.[4]
3. PhSH. This reagent affords the phenyl disulfide.[3]
4. $ClSCO_2Me$, MeOH, 80% yield.[5]



These conditions convert the Acm group to a methyl *S*-sulfenylthiocarbonate group (Scm group), which can be cleaved with dithiothreitol.[6]

5. $ClCOSCl$, $CHCl_3$; $PhNHMe$.[6]



The ***S*-(*N*-methyl-*N*-phenylcarbamoyl)sulfenyl** group (Snm group) produced under these conditions is stable to HF or CF_3SO_3H. Since there are few acid-stable–SH protective groups, the Snm group should prove useful where strong acids are encountered in synthesis.

6. $MeSiCl_3$, Ph_2SO, TFA, 4°, 30 min, 93% yield. These conditions also cleave the Tacm, Bam (benzamidomethyl), *t*-Bu, MeOBn, and MeBn groups in high yield.[7]
7. AgTFA, TFA/anisole (95:5), 3 h, rt; H_2S.[8]
8. $Tl(TFA)_3$, TFA, anisole, 1 h, 66% yield.[9]
9. $AgBF_4$, anisole, TFA, 4°, 1 h, 93% yield. The benzamidomethyl (Bam), 4-methoxybenzyl, and 2,4,6-trimethylbenzyl (Tmb) groups are only partially cleaved under these conditions (87%, 87%, and 73% respectively).[10]
10. I_2, Met, Tyr, His, and Trp are susceptible to overoxidation with iodine if the reaction conditions are not carefully controlled.[11]
11. TFA, triisopropylsilane, 70% yield.[12]

1. D. F. Veber, J. D. Milkowski, S. L. Varga, R. G. Denkewalter, and R. Hirschmann, *J. Am. Chem. Soc.*, **94**, 5456 (1972); J. D. Milkowski, D. F. Veber, and R. Hirschmann, *Org. Synth., Collect., Vol. VI*, 5 (1988).
2. P. Marbach and J. Rudinger, *Helv. Chim. Acta*, **57**, 403 (1974).
3. H. Yajima, K. Akaji, S. Funakoshi, N. Fujii, and H. Irie, *Chem. Pharm. Bull.*, **28**, 1942 (1980).

4. L. Moroder, F. Marchiori, G. Borin, and E. Schoffone, *Biopolymers*, **12**, 493 (1973); A. Fontana, *J. Chem. Soc., Chem. Commun.*, 976 (1975).
5. R. G. Hiskey, N. Muthukumaraswamy, and R. R. Vunnam, *J. Org. Chem.*, **40**, 950 (1975).
6. A. L. Schroll and G. Barany, *J. Org. Chem.*, **54**, 244 (1989).
7. K. Akaji, T. Tatsumi, M. Yoshida, T. Kimura, Y. Fujiwara, and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, 167 (1991).
8. Z. Chen and B. Hemmasi, *Biol. Chem. Hoppe-Seyler*, **374**, 1057 (1993).
9. N. Fujii, A. Otaka, S. Funakoshi, K. Bessho, and H. Yajima, *J. Chem. Soc., Chem. Commun.*, 163 (1987); C. Garcia-Echeverria, M. A. Molins, F. Alberico, M. Pons, and E. Giralt, *Int. J. Pept. Protein Res.*, **35**, 434 (1990).
10. M. Yoshida, K. Akaji, T. Tatsumi, S. IInuma, Y. Fujiwara, T. Kimura, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 273 (1990).
11. B. Kamber, *Helv. Chim. Acta*, **54**, 927 (1971); B. Kamber, A. Hartmann, K. Eisler, B. Riniker, H. Rink, P. Sieber, and W. Rittle, *Helv. Chim. Acta*, **63**, 899 (1980).
12. P. R. Singh, M. Rajopadhye, S. L. Clark, and N. E. Williams, *Tetrahedron Lett.*, **37**, 4117 (1996).

S-Trimethylacetamidomethyl Thioacetal (Tacm–SR): $(CH_3)_3CCONHCH_2SR$

Formation[1,2]

1. $(CH_3)_3CCONHCH_2OH$, TFA, rt, 1 h, >85% yield.

Cleavage

1. I_2, AcOH, EtOH, 25°, 1 h, 100% yield.[1,2] These conditions can result in methionine oxidation.[3]
2. $Hg(OAc)_2$, TFA, 0°, 30 min. The Tacm group is stable to HF (0° 1 h); to 1 *M* CF_3COOH, $PhSCH_3$ (0°, 1 h); to 0.5 *M* NaOH/MeOH (0°, 1 h); to NH_2NH_2; to MeOH; and to Zn/AcOH.[1,2] It is not stable to 25% HBr/AcOH, 2 h, rt.[1] This group was reported to be more useful than the Acm group, because it was less susceptible to by-product formation and oxidation.[2] The Pim (phthalimidomethyl) group is stable under these conditions.[4]
3. $AgBF_4$, anisole, 0°, 1 h, quant. These conditions also cleave the Acm group.[3]

1. Y. Kiso, M. Yoshida, Y. Fujiwara, T. Kimura, M. Shimokura, and K. Akaji, *Chem. Pharm. Bull.*, **38**, 673 (1990).
2. Y. Kiso, M. Yoshida, T. Kimura, Y. Fujiwara, and M. Shimokura, *Tetrahedron Lett.*, **30**, 1979 (1989).
3. M. Yoshida, K. Akaji, T. Tatsumi, S. Iinuma, Y. Fujiwara, T. Kimura, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 273 (1990).
4. Y.-D. Gong and N. Iwasawa, *Chem. Lett.*, 2139 (1994).

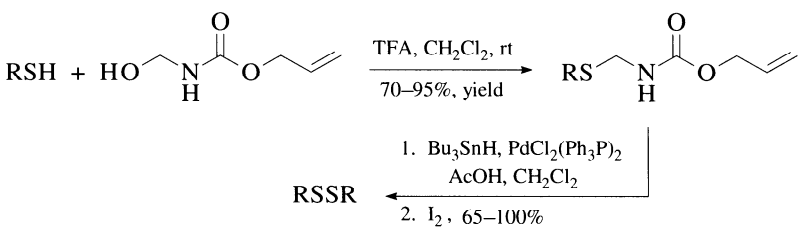
S-Benzamidomethyl Thioacetal (Bam–SR): $RSCH_2NHCOC_6H_5$

S-Benzamidomethyl-*N*-methylcysteine has been prepared as a crystalline derivative ($HOCH_2NHCOC_6H_5$, anhydr. CF_3CO_2H, 25°, 45 min, 88% yield as the trifluoroacetate salt) and cleaved (100% yield) by treatment with mercury(II) acetate (pH 4, 25°, 1 h) followed by hydrogen sulfide. Attempted preparation of *S*-acetamidomethyl-*N*-methylcysteine resulted in noncrystalline material, shown by TLC to be a mixture.[1] The Bam–SR group is also cleaved with $AgBF_4$/TFA, 4°, >1 h[2] and $MeSiCl_3/Ph_2SO$, 4°, 30 min, 100% cleavage.[3] The latter conditions also cleave the Acm, Tacm, *t*-Bu, 4-methoxybenzyl, and 4-methylbenzyl groups.

1. P. K. Chakravarty and R. K. Olsen, *J. Org. Chem.*, **43**, 1270 (1978).
2. M. Yoshida, T. Tatsumi, Y. Fujiwara, S. Iinuma, T. Kimura, K. Akaji, and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 1551 (1990).
3. K. Akaji, T. Tatsumi, M. Yoshida, T. Kimura, Y. Fujiwara, and Y. Kiso, *J. Chem. Soc., Chem. Commun.*, 167 (1991).

S-Allyloxycarbonylaminomethyl Thioacetal (Allocam–SR): $CH_2{=}CHCH_2OC(O)NHCH_2SR$

Formation/Cleavage[1]



1. A. M. Kimbonguila, A. Merzouk, F. Guibe, and A. Loffet, *Tetrahedron Lett.*, **35**, 9035 (1995).

S-Phenylacetamidomethyl Thioacetal (Phacm–SR): $C_6H_5CH_2C(O)NHCH_2SR$

Formation

The Phacm group is introduced by the same methodology as the Acm group[1] [$PhCH_2C(O)NHCH_2OH$, TFMSA].[2]

Cleavage

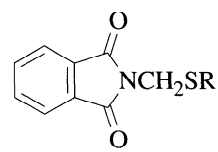
1. Penicillin G. acylase, pH 7.8 buffer, 35°, 30 min to 2 h. These conditions result in isolation of the disulfide, but if β-mercaptoethanol is included in the reaction mixture, the thiol can be isolated.[2]

2. I_2, 80% aq. AcOH. The disulfide is isolated.[2]

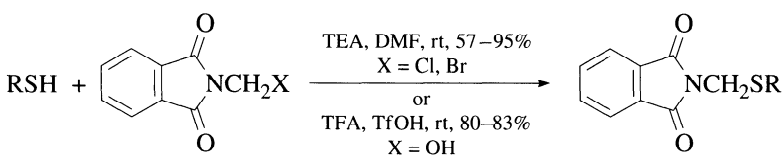
The Phacm group is stable to the following conditions: DIEA–CH_2Cl_2, TFA–CH_2Cl_2, piperidine–DMF, 0.1 *M* TBAF–DMF, and DBU–DMF for 24 h at rt; to HF-anisole or *p*-cresol (9:1) at 0° for 1 h; and to TFA-scavengers (phenol, $HSCH_2CH_2SH$, *p*-cresol, anisole) for 2 h at 25°. It is partially stable (>80%) to TFMSA–TFA–*p*-cresol for 2 h at 25°. These stability characteristics make the group compatible with BOC- or Fmoc-based peptide synthesis.[2]

1. F. Albericio, A. Grandas, A. Porta, E. Pedroso, and E. Giralt, *Synthesis*, 271 (1987).
2. M. Royo, J. Alsina, E. Giralt, U. Slomcyznska, and F. Albericio, *J. Chem. Soc., Perkin Trans. 1*, 1095 (1995).

S-Phthalimidomethyl Thioacetal (Pim–SR):



Formation[1]



Cleavage[1]

1. NH_2NH_2, H_2O, MeOH, 0°–rt 1–2 h; $Hg(OAc)_2$, 2–3 h or $Cu(OAc)_2$, 3–24 h; $HSCH_2CH_2OH$, 71–92% yield. These conditions return the free thiol. The use of $Hg(OAc)_2$ cleaves the Acm (acetamidomethyl) group in the presence of the Pim group.
2. NH_2NH_2, H_2O, MeOH, 0°–rt, 1–2 h; I_2, rt, 1–2 h, 79–89% yield. The disulfide is formed.

1. Y.-D. Gong and N. Iwasawa, *Chem. Lett.*, 2139 (1994).

S-Acetyl-, S-Carboxy-, and S-Cyanomethyl Thioethers: $ArSCH_2X$

X = $-COCH_3$, $-CO_2H$, $-CN$ (Chart 7)

In an attempt to protect thiophenols during electrophilic substitution reactions on the aromatic ring, the three substituted thioethers were prepared. After acetylation of the aromatic ring (with moderate yields), the protective group was converted to the disulfide in moderate yields, 50–60%, by oxidation with hydrogen peroxide/boiling mineral acid, nitric acid, or acidic potassium permanganate. [1]

1. D. Walker, *J. Org. Chem.*, **31**, 835 (1966).

Substituted *S*-Ethyl Derivatives

A thiol, usually under basic catalysis, can undergo Michael addition to an activated double bond, resulting in protection of the sulfhydryl group as a substituted *S*-ethyl derivative. Displacement of an ethyl tosylate by thiolate also affords an *S*-ethyl derivative.

S-(2-Nitro-1-phenyl)ethyl Thioether: $RSCH(C_6H_5)CH_2NO_2$ (Chart 7)

Formation

1. $PhCH{=}CHNO_2$, *N*-methylmorpholine, pH 7–8, 10 min, 70% yield.[1]

Cleavage

The protective group is removed by mildly alkaline conditions that do not cleave methyl or benzyl esters. The group is stable to CF_3COOH, HCl–AcOH, and HBr–AcOH. A polymer-bound version of this group has also been developed.[2]

S-2-(2,4-Dinitrophenyl)ethyl Thioether (Dnpe-SR):

Formation

2-(2,4-Dinitrophenyl)ethyl tosylate, DIPEA, DMF, 63% yield.[3]

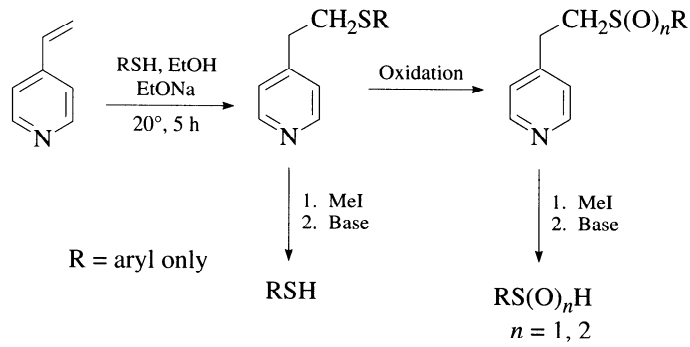
Cleavage

Piperidine, DMF (1:1), 30 min, 25°, 57–90% yield.[3]

1. G. Jung, H. Fouad, and G. Heusel, *Angew. Chem., Int. Ed. Engl.*, **14**, 817 (1975).
2. G. Heusel and G. Jung, *Liebigs Ann. Chem.*, 1173 (1979).
3. M. Royo, C. Garcia-Echeverria, E. Giralt, R. Eritja, and F. Albericio, *Tetrahedron Lett.*, **33**, 2391 (1992).

S-2-(4′-Pyridyl)ethyl Thioether: $C_4H_4NCH_2CH_2SR$

Formation[1]*/Cleavage*[2]



The intermediate sulfides can be oxidized to the corresponding sulfoxides and sulfones and then liberated to give sulfenic and sulfinic acids.

1. A. R. Katritzky, I. Takahashi, and C. M. Marson, *J. Org. Chem.*, **51**, 4914 (1986).
2. A. R. Katritzky, G. R. Khan, and O. A. Schwarz, *Tetrahedron Lett.*, **25**, 1223 (1984).

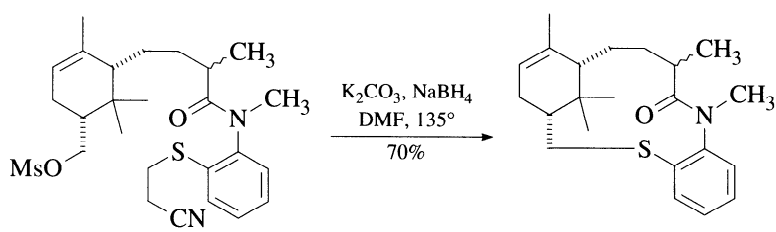
S-2-Cyanoethyl Thioether: $NCCH_2CH_2SR$

Formation

1. $BrCH_2CH_2CN$, K_2CO_3, DMF.[1]

Cleavage

1. The 2-cyanoethyl group was cleaved from an aromatic sulfide with K_2CO_3/$NaBH_4$ (DMF, 135°, 70% yield).[2]



2. Concd. NH_4OH, rt, quant.[1]
3. *t*-BuOK, DMF, 50–94%.[3]

1. M. S. Christopherson and A. D. Broom, *Nucleic Acids Res.*, **19**, 5719 (1991).

2. Y. Ohtsuka and T. Oishi, *Tetrahedron Lett.*, **27**, 203 (1986).
3. A. Kakehi, S. Ito, N. Yamada, and K. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **63**, 829 (1990).

S-2-(Trimethylsilyl)ethyl Thioether: $TMSCH_2CH_2SR$

Cleavage

1. $Bu_4N^+F^-$, 3Å, THF, rt, >53% yield.[1]
2. $MeSS^+Me_2\ BF_4^-$ forms a disulfide in 92% yield that is cleaved to the thiol with $Ph_3P/MeOH/H_2O$ in 90% yield.[2]

1. M. Koreeda and W. Yang, *J. Am. Chem. Soc.*, **116**, 10793 (1994).
2. M. B. Anderson, M. G. Ranasinghe, J. T. Palmer, and P. L. Fuchs, *J. Org. Chem.*, **53**, 3125 (1988).

S-2,2-Bis(carboethoxy)ethyl Thioether: $RSCH_2CH(COOC_2H_5)_2$ (Chart 7)

Formation

1. $CH_2{=}C(CO_2Et)_2$, EtOH, 1 h, 74% yield.[1]

Cleavage

1. 1 *N* KOH, EtOH, 20°, 5–10 min, 80% yield. *S*-2,2-Bis(carboethoxy)ethyl thioether, stable to acidic reagents such as trifluoroacetic acid and hydrogen bromide/acetic acid, has been used in a synthesis of glutathione.[1]

1. T. Wieland and A. Sieber, *Justus Liebigs Ann. Chem.*, **722**, 222 (1969); *idem*, *ibid.*, **727**, 121 (1969).

S-(1-*m*-Nitrophenyl-2-benzoyl)ethyl Thioether: $ArSCH(C_6H_4\text{–}m\text{-}NO_2)CH_2COC_6H_5$

An *S*-(1-*m*-nitrophenyl-2-benzoyl)ethyl thioether was used to protect thiophenols during electrophilic substitution reactions of the benzene ring.[1]

Formation

1. $PhCOCH{=}CHC_6H_4\text{–}m\text{-}NO_2$, piperidine, benzene, 96% yield.[1]

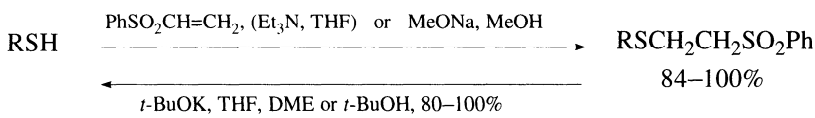
Cleavage

1. $Pb(OAc)_2$, EtOH, pH 8–10; dil HCl, 77% yield.[1]

1. A. H. Herz and D. S. Tarbell, *J. Am. Chem. Soc.*, **75**, 4657 (1953).

S-2-Phenylsulfonylethyl Thioether and *S*-1-(4-Methylphenylsulfonyl)-2-methylprop-2-yl Thioether: $PhSO_2CH_2CH_2SR$ and $4\text{-}CH_3C_6H_4SO_2CH_2C(CH_3)_2SR$

Formation/Cleavage[1,2]



1. Y. Kuroki and R. Lett, *Tetrahedron Lett.*, **25**, 197 (1984).
2. L. Horner and H. Lindel, *Phosphorus Sulfur*, **15**, 1 (1983).

Silyl Thioethers

Silyl-derived protective groups are also used to mask the thiol function. A complete compilation is not given here, since silyl derivatives are described in the section on alcohol protection. The formation and cleavage of silyl thioethers proceed analogously to those of simple alcohols. The Si–S bond is weaker than the Si–O bond, and therefore, sulfur derivatives are more susceptible to hydrolysis. For the most part, silyl ethers are rarely used to protect the thiol function, because of their instability. Silyl ethers have been used for *in situ* protection of the –SH group during amide formation.[1] The use of the sterically demanding and thus more stable **triisopropylsilyl** thioether may prove worthwhile.[2]

1. E. W. Abel, *J. Chem. Soc.*, 4933 (1961); L. Birkofer, W. Konkol, and A. Ritter, *Chem. Ber.*, **94**, 1263 (1961).
2. J. C. Arnould, M. Didelot, C. Cadilhac, and M. J. Pasquet, *Tetrahedron Lett.*, **37**, 4523 (1996).

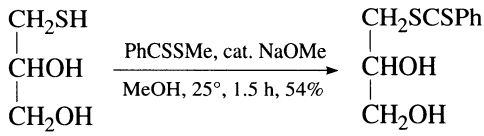
THIOESTERS

S-Acetyl Derivative: $RSCOCH_3$

S-Benzoyl Derivative: $RSCOC_6H_5$ (Chart 7)

Formation

1. Ac_2O, $KHCO_3$, 55% yield.[1]
2. BzCl, NaOH, $KHCO_3$, 0–5°, 30 min., 50% yield.[2]



The base-catalyzed reaction of thiothreitol with methyl dithiobenzoate selectively protects a thiol group as an *S*-thiobenzoyl derivative in the presence of a hydroxyl group.[2]

Cleavage

1. 0.2 *N* NaOH, N_2, 20°, 2–15 min, 100% yield.[1]
2. Aqueous NH_3, N_2, 20°, 95–100% yield.[1]
3. HBr, AcOH, 25°, 30 min, 5% to a substantial amount.[1]
4. CF_3CO_2H, phenol, reflux, 30 min, 2–5% yield. In this case, an *S*–Cbz group is removed.[1]
5. $Fe(NO_3)_3$–Clayfen.[3]
6. NaSMe, MeOH, 23°, 81–95% yield.[4] This procedure is chemoselective for removal of a thioacetate in the presence of an acetate.

Two disadvantages are associated with the use of *S*-acetyl or *S*-benzoyl derivatives in peptide syntheses: (a) base-catalyzed hydrolysis of *S*-acetyl- and *S*-benzoylcysteine occurs with β-elimination to give olefinic side products, CH_2=C–(NHPG)CO–;[5] (b) the yields of peptides formed by coupling an unprotected amino group in an *S*-acylcysteine are low because of prior S–N acyl migration.[6]

An *S*-acetyl group is stable to oxidation of a double bond by ozone (–20°, 5.5 h, 73% yield).[7]

S-Trifluoroacetyl Derivative: $RSCOCF_3$

Formation

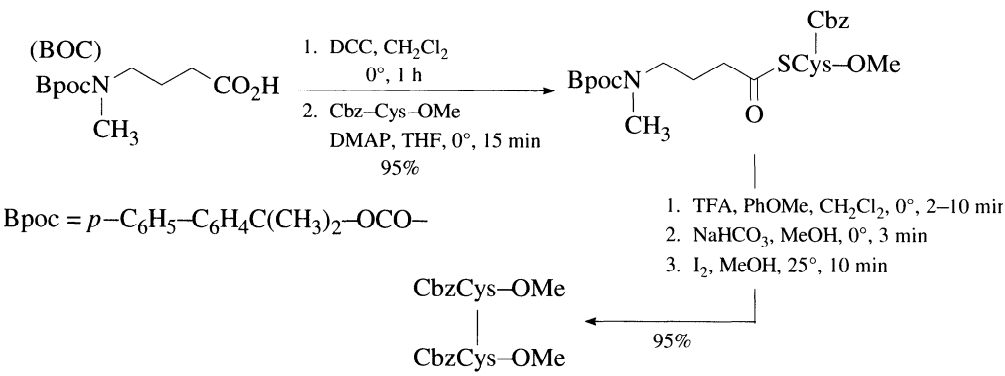
1. $CF_3COSC_6F_5$, Pyr, DMF, 75% yield.[8]

1. L. Zervas, I. Photaki, and N. Ghelis, *J. Am. Chem. Soc.*, **85**, 1337 (1963).
2. E. J. Hedgley and N. H. Leon, *J. Chem. Soc. C*, 467 (1970).
3. H. M. Meshram, *Tetrahedron Lett.*, **34**, 2521 (1993).
4. O. B. Wallace and D. M. Springer, *Tetrahedron Lett.*, **39**, 2693 (1998).
5. R. G. Hiskey, R. A. Upham, G. M. Beverly, and W. C. Jones, Jr., *J. Org. Chem.*, **35**, 513 (1970).
6. R. G. Hiskey, T. Mizoguchi, and T. Inui, *J. Org. Chem.*, **31**, 1192 (1966).
7. I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978).

8. L. M. Gayo and M. J. Suto, *Tetrahedron Lett.*, **37**, 4915 (1996).

S-N-[[(p-Biphenylyl)isopropoxy]carbonyl]-N-methyl-γ-aminothiobutyrate: $BpocN(CH_3)CH_2CH_2CH_2COSR$ **and S-N-(t-Butoxycarbonyl)-N-methyl-γ-aminothiobutyrate:** $BOCN(CH_3)CH_2CH_2CH_2COSR$

Formation/Cleavage[1]



Deprotection is effected only by step 1 (TFA, PhOMe, CH_2Cl_2, 0°, 2–10 min).

1. N. G. Galakatos and D. S. Kemp, *J. Org. Chem.*, **50**, 1302 (1985).

Thiocarbonate Derivatives

When cysteine reacts with an alkyl or aryl chloroformate, both the –SH and –NH groups are protected, as a thiocarbonate and as a carbamate, respectively. Selective or simultaneous removal of the protective groups is possible. (See cleavage conditions 3–6 for an *S*-benzyloxycarbonyl derivative, page 485.)

S-2,2,2-Trichloroethoxycarbonyl Derivative: $RSCOOCH_2CCl_3$

Cleavage

1. Electrolysis, –1.5 V, $LiClO_4$, CH_3OH, 90% yield. The conditions can be adjusted to form either the sulfide or disulfide.[1]

1. M. F. Semmelhack and G. E. Heinsohn, *J. Am. Chem. Soc.*, **94**, 5139 (1972).

S-t-Butoxycarbonyl Derivative (BOC–SR): $RSCOOC(CH_3)_3$

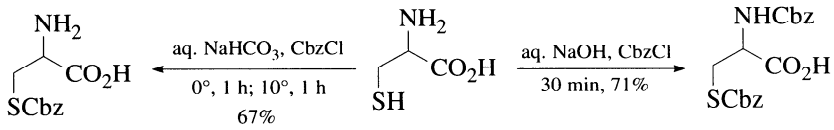
t-Butyl chloroformate reacts with cysteine to protect both the amine and thiol groups; as with *N,S*-bis(benzyloxycarbonyl)cysteine, selective or simultaneous

removal of the *N*- or *S*-protective groups can be effected.[1] Treatment with HCl/EtOAc efficiently cleaves the S–BOC group.[2]

1. M. Muraki and T. Mizoguchi, *Chem Pharm. Bull.*, **19**, 1708 (1971).
2. F. S. Gibson, S. C. Bergmeier, and H. Rapoport, *J. Org. Chem.*, **59**, 3216 (1994).

S-Benzyloxycarbonyl Derivative (RS-Cbz, RS-Z): $RSCOOCH_2C_6H_5$

Formation[1]



Cleavage

1. Concd. NH_4OH, 25°, 1 h, 90% yield.[1]
2. Na, NH_3, 62% yield.[1]
3. 0.1 *N* $NaOCH_3$, CH_3OH, N_2, 30 min–3 h, 100% yield.[2] An *S*-benzoyl group is removed (95–100% yield) in 5–10 min.
4. CF_3COOH, reflux, 30 min, ca. quant.[2] An *N*-Cbz group is also removed under these conditions.
5. 2 *N* HBr, AcOH, 25°, 30 min.[2,3] The *S*-Cbz group is removed slowly under these conditions, but the *N*-Cbz group is completely cleaved, thus providing some selectivity in the protection scheme for cysteine.
6. Electrolysis, –2.6 V, $R_4N^+X^-$, DMF.[4] Both an *N*-Cbz group and an *S*-Cbz group are removed under these conditions.

1. A. Berger, J. Noguchi, and E. Katchalski, *J. Am. Chem. Soc.*, **78**, 4483 (1956).
2. L. Zervas, I. Photaki, and N. Ghelis, *J. Am. Chem. Soc.*, **85**, 1337 (1963).
3. M. Sokolovsky, M. Wilchek, and A. Patchornik, *J. Am. Chem. Soc.*, **86**, 1202 (1964).
4. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).

S-*p*-Methoxybenzyloxycarbonyl Derivative: $RSCOOCH_2C_6H_4$–*p*-OCH_3

S-*p*-Methoxybenzyloxycarbonylcysteine has been prepared in low yield (30%). It has been used in peptide syntheses, but is very labile to acids and bases.[1]

1. I. Photaki, *J. Chem. Soc. C*, 2687 (1970).

Thiocarbamate Derivatives

Thiocarbamates, formed by reaction of a thiol with an isocyanate, are stable in acidic and neutral solutions and are readily cleaved by basic hydrolysis. The

β-elimination that can occur when an *S*-acyl group is removed with base from a cysteine derivative does not occur under the conditions needed to cleave a thiocarbamate.[1]

S-(*N*-Ethylcarbamate): $RSCONHC_2H_5$ (Chart 7)

Formation[1]

1. EtN=C=O, pH 1→ pH 6, 20°, 70 h, 67% yield.

Cleavage

1. 1 *N* NaOH, 20°, 20 min, 100% yield.[1]
2. NH_3 or NH_2NH_2, methanol, 20°, 2 h, 100% yield.[1]
3. Na/NH_3, –30°, 3 min, 100% yield.[1]
4. $Hg(OAc)_2$, H_2O, CH_3OH, 30 min; H_2S, 4 h, 79% yield.[2]
5. $AgNO_3$, H_2O, CH_3OH; concd. HCl, 3 h, 62% yield.[2]

This protective group is stable to acidic hydrolysis (4.5 *N* HBr/HOAc; 1 *N* HCl; CF_3CO_2H, reflux). There is no evidence of S → N acyl migration in *S-(N*-ethylcarbamates) (RS = cysteinyl).[1] Oxidation of *S-(N*-ethylcarbamoyl)cysteine with performic acid yields cysteic acid.[2]

1. St. Guttmann, *Helv. Chim. Acta*, **49**, 83 (1966).
2. H. T. Storey, J. Beacham, S. F. Cernosek, F. M. Finn, C. Yanaihara, and K. Hofmann, *J. Am. Chem. Soc.*, **94**, 6170 (1972).

S-(*N*-Methoxymethylcarbamate): $RSCONHCH_2OCH_3$

Formation[1]

1. $CH_3OCH_2N=C=O$, pH 4–5, 2 min, 100% yield.

At pH 4–5, the reaction is selective for the protection of thiol groups in the presence of α- or ε-amino groups.

Cleavage[1]

1. At pH 9.6, a cysteine derivative is cleaved in 100% yield and a glutathione derivative in 80% yield.

1. H. Tschesche and H. Jering, *Angew. Chem., Int. Ed. Engl.*, **12**, 756 (1973).

MISCELLANEOUS DERIVATIVES

Unsymmetrical Disulfides

A thiol can be protected by oxidation (with O_2; H_2O_2; I_2;···) to the corresponding symmetrical disulfide, which subsequently can be cleaved by reduction: [Sn/HCl; Na/xylene, Et_2O, or NH_3; $LiAlH_4$; $NaBH_4$; or thiols such as $HO(CH_2)_2SH$]. Unsymmetrical disulfides have also been prepared and are discussed.

S-Ethyl Disulfide: $RSSC_2H_5$ (Chart 7)

Formation

1. EtS(O)SEt, –70°, 1 h, 80–90% yield.[1]

Cleavage

1. PhSH, >50° or $HSCH_2CO_2H$, 45°, 15 h, quant.[2] The *S*-ethyl disulfide is stable to acid-catalyzed hydrolysis (CF_3CO_2H) of carbamates and to ammonolysis (25% NH_3/CH_3OH).[2]

1. D. A. Armitage, M. J. Clark, and C. C. Tso, *J. Chem. Soc., Perkin Trans. 1*, 680 (1972).
2. N. Inukai, K. Nakano, and M. Murakami, *Bull. Chem. Soc. Jpn.*, **40**, 2913 (1967).

S-*t*-Butyl Disulfide: $RSSC(CH_3)_3$

Formation

1. $CH_3OC(O)SCl$, 0–5°, 1.5 h; *t*-BuSH, MeOH, 5 days, 97% crude, 46% pure.[1] The reaction proceeds through an *S*-sulfenyl thiocarbonate.
2. *t*-$BuO_2CNHN(S$-*t*-$Bu)CO_2$–*t*-Bu, H_2O.[2]

Cleavage

1. $NaBH_4$.[3]
2. Bu_3P, trifluoroethanol/water (95/5).[4]

1. L. Field and R. Ravichandran, *J. Org. Chem.*, **44**, 2624 (1979).
2. E. Wünsch, L. Moroder, and S. Romani, *Hoppe-Seyler's Z. Physiol. Chem.*, **363**, 1461 (1982).
3. E. Wünsch and R. Spangenberg, in *Peptides, 1969*, E. Schoffone, Ed., North Holland, Amsterdam, p. 1971.

4. R. Ramage and A. S. J. Stewart, *J. Chem. Soc., Perkin Trans. 1*, 1947 (1993).

Substituted *S*-Phenyl Disulfides: $RSSC_6H_4$–Y

Three substituted *S*-phenyl unsymmetrical disulfides have been prepared, **i**,[1] **ii**,[2] and **iii**[3] — compounds **i** and **ii** by reaction of a thiol with a sulfenyl halide, compound **iii** from a thiol and an aryl thiosulfonate ($ArSO_2SAr$). The disulfides are cleaved by reduction ($NaBH_4$) or by treatment with excess thiol ($HSCH_2CH_2OH$).

$RSS–C_6H_3–2\text{-}NO_2\text{-}4\text{-}R'$ **i** ($R' = H, NO_2$) $RSS–C_6H_4–2\text{-}N{=}N–C_6H_5$ **ii** $RSS–C_6H_4–2\text{-}COOH$ **iii**

1. A. Fontana, E. Scoffone, and C. A. Benassi, *Biochemistry*, **7**, 980 (1968); A. Fontana, *J. Chem. Soc., Chem. Commun.*, 976 (1975).
2. A. Fontana, F. M. Veronese, and E. Scoffone, *Biochemistry*, **7**, 3901 (1968).
3. L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971).

Sulfenyl Derivatives

S-Sulfonate Derivative: $RSSO_3^-$

Formation

1. Na_2SO_3, cat. cysteine, O_2, pH 7–8.5, 1 h, quant.[1]

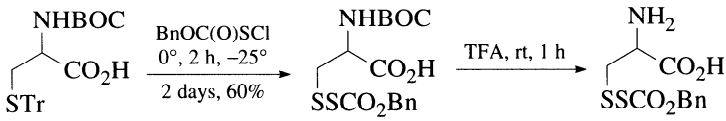
Cleavage

1. $HSCH_2CH_2OH$, pH 7.5, 25°, 2 h, 100% yield.[1]
2. $NaBH_4$.[1] *S*-Sulfonates are stable at pH 1–9; they are unstable in hot acidic solutions and in 0.1 *N* sodium hydroxide.

1. W. W.-C. Chan, *Biochemistry*, **7**, 4247 (1968).

S-Sulfenylthiocarbonate: RSSCOOR′

A number of *S*-sulfenylthiocarbonates have been prepared to protect thiols. A benzyl derivative, R′=CH_2Ph, is stable to trifluoroacetic acid (25°, 1 h), but not to HBr/AcOH, and provides satisfactory protection during peptide syntheses;[1] a *t*-butyl derivative, R′ = *t*-Bu, is too labile in base to provide protection.[1] A methyl derivative, R′=CH_3, has been used to protect a cysteine fragment that is subsequently converted to a cystine.[2]



1. K. Nokihara and H. Berndt, *J. Org. Chem.*, **43**, 4893 (1978).
2. R. G. Hiskey, N. Muthukumaraswamy, and R. R. Vunnam, *J. Org. Chem.*, **40**, 950 (1975).

S-3-Nitro-2-pyridinesulfenyl Sulfide (Npys–SR): 3-NO_2–C_5H_3NSSR

These sulfides are prepared from other sulfur-protected cysteine derivatives by reaction with the sulfenyl chloride.[1] The Npys group can also be introduced directly by treatment of the thiol with NpysCl.[2]

Conversion of Conventional *S*-Protective Groups into the NpysSR Derivative[1]

Starting Material	Npys–X, Eq.	Conditions	% Yield
Boc–Cys(Bn)–OH	Cl, 1.2	rt, 24 h, CH_2Cl_2	No reaction
Boc–Cys(MeOBn)–OH[3]	Cl, 1.2	0°, 30 min, CH_2Cl_2	92
Boc–Cys(Me_2Bn)–OH	Cl, 1.2	0°, 30 min, CH_2Cl_2	90
Z–Cys(MeOBn)–Phe–Phe–Gln–Asn–O–*t*-Bu	Cl, 1.2	rt, 30 min, CH_2Cl_2, CF_3COOH (1:1)	85
Fmoc–Cys(*t*-Bu)–OH	Cl, 1.2	0°, 30 min, CH_2Cl_2	80
Boc–Cys(Tr)–OH	Cl, 1.2	–30°, 3 h, CH_2Cl_2	91
Boc–Cys(Acm)–OH	Cl, 1.2	0°, 30 min, AcOH	63
Z–Cys(Bn)–OH	Br, 2.0	rt, 10 h, CH_2Cl_2	21
Z–Cys(Bn)–OH	Cl, 2.0	rt, 5 h, CF_3CH_2OH	61
Z–Cys(Bn)–OH	Br, 2.4	rt, 3 h, CF_3CH_2OH, AcOH (10:1)	73
Z–Cys(Bn)–Pro–Leu–$GlyNH_2$	Br, 2.4	rt, 3 h, CF_3CH_2OH, AcOH (10:1)	70

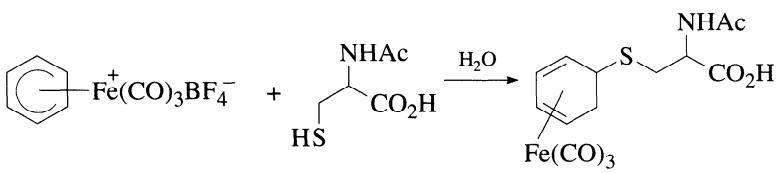
The Npys group can be cleaved reductively with Bu_3P, H_2O, or mercaptoethanol. It has also been cleaved with 2-mercaptopyridine, 2-mercaptomethylimidazole, or 2-mercaptoacetic acid in methanol/acetic acid. Selective cleavage of the *O*-Npys bond over the *S*-Npys bond can be achieved with the aromatic thiols.[4] The Npys group is stable to CF_3COOH (24 h), 4 *M* HCl/dioxane (24 h), and HF (1 h).[2] The related reagent, 2-pyridinesulfenyl chloride, has also been proposed as a useful reagent for the deprotection of the *S*-trityl, *S*-diphenylmethyl, *S*-acetamidomethyl, *S*-*t*-butyl, and ***S*-*t*-butylsulfenyl** groups, but it is very susceptible to hydrolysis.[5]

1. R. Matsueda, S. Higashida, R. J. Ridge, and G.R. Matsueda, *Chem. Lett.*, 921 (1982).
2. R. Matsueda, T. Kimura, E. T. Kaiser, and G. R. Matsueda, *Chem. Lett.*, 737 (1981).

3. O. Ploux, M. Caruso, G. Chassaing, and A. Marquet, *J. Org. Chem.*, **53**, 3154 (1988).
4. O. Rosen, S. Rubinraut, and M. Fridkin, *Int. J. Pept. Protein Res.*, **35**, 545 (1990).
5. J. V. Castell and A. Tun-Kyi, *Helv. Chim. Acta*, **62**, 2507 (1979).

S-[Tricarbonyl[1,2,3,4,5-η]-2,4-cyclohexadien-1-yl]-iron(1+) Thioether: $[(\eta\text{-}^5C_6H_7)Fe(CO)_3]SR$

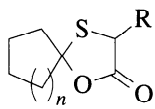
Formation



Cleavage

Treatment with HBF_4 in $CHCl_3$ liberates the thiol and returns the derivatizing agent, $[(\eta\text{-}^5C_6H_7)Fe(CO)_3]^+ BF_4^-$ [tricarbonyl[1,2,3,4,5-η]-2,4-cyclohexadien-1-yl-iron(1+) tetrafluoroborate] as a precipitate.[1]

1. S. Fu, J. A. Carver, and L. A. P. Kane-Maguire, *J. Organomet. Chem.*, **454**, C11 (1993).

Oxathiolones:  $n = 1, 2$

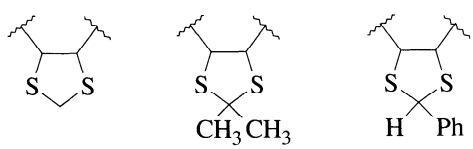
Oxathiolones are formed by heating a ketone with the mercaptocarboxylic acid in the presence of TsOH. They are cleaved by either acid (TFA, H_2O, THF) or base (NaOH, acetone) hydrolysis.[1]

1. L. M. Gustavson, D. S. Jones, J. S. Nelson, and A. Srinivasan, *Synth. Commun.*, **21**, 249 (1991).

Protection for Dithiols

Dithio Acetals and Ketals

S,S′-Methylene (i), S, S′-Isopropylidene (ii), and S, S′-Benzylidene (iii), Derivatives



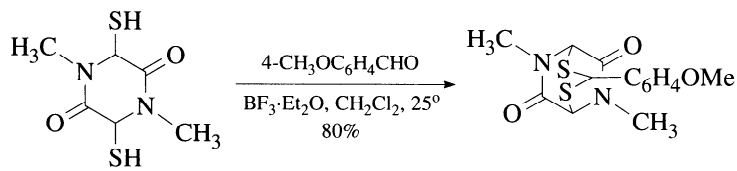
i **ii** **iii**

Dithiols, like diols, have been protected as *S,S′*-methylene,[1] *S,S′*-isopropylidene,[2] and *S,S′*-benzylidene[3] derivatives, formed by reaction of the dithiol with formaldehyde, acetone, or benzaldehyde, respectively. The methylene and benzylidene derivatives are cleaved by reduction with sodium/ammonia. The isopropylidene[2] and benzylidene[3] derivatives are cleaved by mercury(II) chloride; with sodium/ammonia, the isopropylidene derivative is converted to a monothio ether, $HSCHRCHRSCHMe_2$.[1]

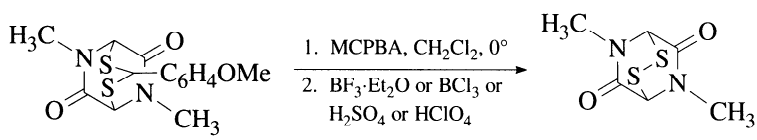
1. E. D. Brown, S. M. Igbal, and L. N. Owen, *J. Chem. Soc., C* 415 (1966).
2. E. P. Adams, F. P. Doyle, W. H. Hunter, and J. H. C. Nayler, *J. Chem. Soc.*, 2674 (1960).
3. L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 2938 (1950).

S,S′-p-Methoxybenzylidene Derivative: $(RS)_2CHC_6H_4$–4-OCH_3

Formation[1]



Cleavage[1]



The preceding epidithioketopiperazine is present in natural products, including the gliotoxins and sporidesmins.[1]

1. Y. Kishi, T. Fukuyama, and S. Nakatusuka, *J. Am. Chem. Soc.*, **95**, 6490 (1973).

Protection for Sulfides

Since sulfides tend to react with electrophiles, a method for protecting sulfides could be quite useful. Sulfoxides can be used to protect sulfides and are easily formed by a variety of oxidants. Sulfides can be regenerated with thiols,[1] $SiCl_4$ (0°, 15 min, TFA, anisole),[2] $LiBH_4/Me_3SiCl$,[3] and $DMF{\cdot}SO_3/HSCH_2CH_2SH$ (DMF, Pyr, rt, 85% yield).[4]

Sulfides can also be protected as sulfonium salts.

S-Methylsulfonium Salt: $R_2S^+CH_3\ X^-$

Formation

1. $CH_3OSO_2CF_3$, CH_2Cl_2, 99% yield.[5]
2. MeOTs, EtOAc, rt, 4 days, 85% yield.[6]

Cleavage

1. DMF, Et_3N, $HSCH_2CH_2OH$, rt, 78% yield.[6]
2. $LiAlH_4$, THF.[5]

   A methylsulfonium salt is stable to NH_3/MeOH and to TFA, but not to hydrogenolysis (H_2/Pd–C).[6]

S-Benzyl- and *S*-4-Methoxybenzylsulfonium Salt: $R_2S^+CH_2Ph\ X^-$

Formation

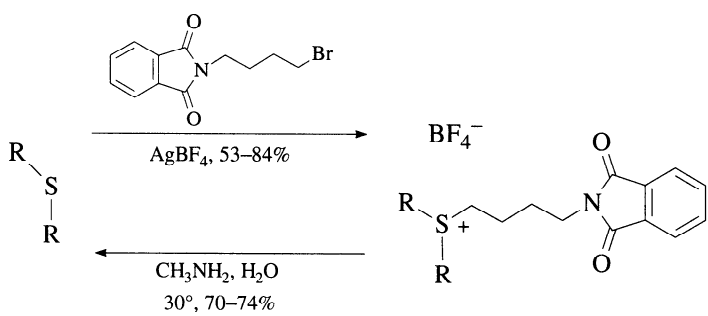
1. $C_6H_5CH_2OTf$, CH_3CN.[7]
2. $4\text{-}MeOC_6H_4CH_2Cl$, $AgBF_4$, CH_3CN, 97–99% yield.[8]

Cleavage

The benzylsulfonium salt is cleaved by hydrogenolysis (H_2/Pd–C, MeOH);[7] the 4-methoxybenzylsulfonium salt is cleaved by methylamine (100%).[8]

S-1-(4-Phthalimidobutyl)sulfonium Salt

Formation/Cleavage[8]



1. N. Fujii, A. Otaka, S. Funakoshi, H. Yajima, O. Nishimura, and M. Fujino, *Chem. Pharm. Bull.*, **34**, 869 (1986).
2. Y. Kiso, M. Yoshida, T. Fujisaki, T. Mimoto, T. Kimura, and M. Shimokura, *Pept. Chem., 1986*, **24th**, 205 (1987); *Chem. Abstr.*, **108:** 112924j (1988).

3. A. Giannis and K. Sandhoff, *Angew. Chem., Int. Ed. Engl.*, **28**, 218 (1989).
4. S. Futaki, T. Taike, T. Yagami, T. Akita, and K. Kitagawa, *Tetrahedron Lett.*, **30**, 4411 (1989).
5. V. Cere, A. Guenzi, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **45**, 261 (1980).
6. M. Bodanszky and M. A. Bednareck, *Int. J. Pept. Protein Res.*, **20**, 408 (1982).
7. R. C. Roemmele and H. Rapoport, *J. Org. Chem.*, **54**, 1866 (1989).
8. J. T. Doi and G. W. Luehr, *Tetrahedron Lett.*, **26**, 6143 (1985).

S–P Derivatives

S-(Dimethylphosphino)thioyl Group (Mpt–SR): $(CH_3)_2P(S)SR$

S-(Diphenylphosphino)thioyl Group (Ppt-SR): $Ph_2P(S)SR$

Formation

1. MptCl, (*i*-Pr)$_2$EtN, $CHCl_3$, 79% yield. The Mpt group on the nitrogen in cysteine can be selectively removed with HCl/Ph_3P, leaving the *S*–Mpt group intact.[1]

Cleavage

1. $AgNO_3$, H_2O, Pyr, 0°, 1 h; H_2S, 100% yield.[1]
2. KF, 18-crown-6 or $Bu_4N^+F^-$, CH_3CN, MeOH, 88% yield.[2]
   The related *S*-(diphenylphosphino)thioyl group (Ppt group) has also been cleaved using these conditions.[3] The Mpt derivative of cysteine is not stable to DBU; it forms dehydroalanine. The Mpt group is stable to TFA and to 1 *M* HCl, but not to HBr/AcOH or 6 *M* HCl.[1]
3. $Bu_4N^+F^-$, THF, AcOH, >76% yield.[4]

1. M. Ueki and K. Shinozaki, *Bull. Chem. Soc. Jpn.*, **56**, 1187 (1983).
2. M. Ueki and K. Shinozaki, *Bull. Chem. Soc. Jpn.*, **57**, 2156 (1984).
3. L. Horner, R. Gehring, and H. Lindel, *Phosphorus Sulfur*, **11**, 349 (1981).
4. M. Ueki, H. Takeshita, A. Sacki, H. Komatsu, and T. Katoh, *Pept. Chem. 1994, 32nd*, 173 (1995), *Chem. Abstr.*, **123:** 257332j (1995).